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DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,265	SPRINGER ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 06 August 2003.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 25-30, 73-80 and 82-93 is/are pending in the application.
 4a) Of the above claim(s) 89-93 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 25-30, 73-80 and 82-88 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
 a) The translation of the foreign language provisional application has been received.
 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____	6) <input type="checkbox"/> Other: _____

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/06/03 has been entered.
2. Claims 25-30, 73-80 and 82-93 are pending.
3. Claims 89-93 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.
4. Claims 25-30, 73-80 and 82-88 are under examination as they read on an antibody that selectively binds to a modified integrin I-domain in the open conformation.
5. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
 6. Claims 26-29, 73-80, 82 and 85-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
 - A. “The antibody of claim 25” recited in claims 26-29, has no antecedent basis in base claim 25, base claim 25 recites antibody, or antigen binding fragment thereof. It is suggested that the preamble of claims 26-29 be changed to “ The antibody or an antigen binding fragment thereof of claim 25.....”.
 - B. “The antibody of any one of claims 25, 30, or 79” recited in claim 82 has no antecedent basis in base claims 25, 30, or 79. Base claims 25, 30, and 79 recite antibody, or antigen binding fragment thereof. It is suggested that the claim be change to “The antibody or an antigen binding fragment thereof of any one of claims 25, 30, or 79, wherein said antibody is a monoclonal antibody”.
 - C. Claim 76 is indefinite in that recitation of the “a portion of a human antibody and a portion of a non-human antibody”. It is unclear if the “portion” refers to any antibody portion or portions containing the antigen-binding domain of the antibody. Further, it is not clear what portion derived from a human antibody and what portion derived from non-human antibody.
 7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 25-30, 73-80 and 82-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase “relative to a modified integrin I-domain in the closed conformation” claimed in claim 25, line 3, the phrase “relative to an integrin I-domain in the closed conformation” claimed in claim 30, line 3, the phrase “relative to an LFA-1 domain in the closed conformation” claimed in claim 75, lines 3-4, the phrase “but not to an integrin I-domain in the closed conformation” claimed in claim 83, line 2, the phrase “but not to a modified integrin I-domain that is locked in the closed conformation by the substitutions 289C/K294C” in claimed in claim 84, lines 2-3, and the phrase “but not to a modified integrin I-domain in the closed conformation” claimed in claim 85, lines 2-3, represent a departure from the specification and the claims as originally filed.

Applicant’s amendment filed 8-06-03 does not point to the specification for support for the newly added limitations “relative to a modified integrin I-domain in the closed conformation”, “relative to an integrin I-domain in the closed conformation”, “relative to an LFA-1 domain in the closed conformation”, “but not to an integrin I-domain in the closed conformation”, “but not to a modified integrin I-domain that is locked in the closed conformation by the substitutions 289C/K294C” and “but not to a modified integrin I-domain in the closed conformation” as claimed in claims 23, 30, 75, and 83-84. However, the specification does not provide a clear support for such limitations. The instant claims now recite limitations, which were not clearly disclosed in the specification and recited in the claims as originally filed.

9. Claims 25-30, 73-80 and 82-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not provide **enablement** for a recombinant antibody or an antigen binding fragment thereof, which specifically binds to a modified integrin I-domain in the open conformation, “relative to a modified integrin I-domain in the closed conformation” in claims 25, 30 and 75, an antibody or an antigen binding fragment thereof, which binds to an integrin I-domain in the open conformation but not to an integrin I-domain in the closed conformation in claim 83, an antibody or an antigen binding fragment thereof, which binds to an integrin I-domain in the open conformation but not to a modified integrin I-domain that is locked in the closed conformation by the substitutions of 289C/K294C in claim 84, which binds to a modified integrin I-domain in the open conformation but not to a modified integrin I-domain in the closed conformation in claim 86. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

One cannot extrapolate the teachings of the specification to the scope of the claims because the product claims are drawn to the antibody that binds to integrin I-domain in the open conformation but not closed conformation. The specification on page 67, last paragraph discloses that the monoclonal antibodies BL5, F8.8, CBRLFA-1/9, May.03, TS1/22 and TS2/6 strongly inhibited binding of both wild type and mutant K287C/K294C, and the levels of

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inhibition to wild type LFA-1 and the mutant were similar. Further the specification discloses that monoclonal antibodies TS1/11 and TS1/12 inhibited >90% binding of transfectants that express wild type LFA1, these antibodies showed reduced inhibition on binding of mutant K287C/D294C (40-60%). Furthermore, Monoclonal antibodies TS2/14, 25-3-1 and CBRLFA-1/1 show >90% inhibition on binding of wild type but had no to little inhibition on mutant K287C/K294C binding to ICAM-1. Finally, Table 3 in the specification at page 69, provides no single example of an antibody that binds the open conformation but not the closed conformation of the LFA-1. In the contrary Table 3, provides antibody that binds either to both closed and opened conformation or to the closed conformation but not to the opened conformation. The claimed products do not have the biological properties representative of what is being claimed, and applicant has not enabled any of these types of antibodies because it has not been shown that these antibodies are capable of functioning as that which is being claimed.

It is now known that the specificity of an antibody for a given antigen is encoded within a 5-15 amino acid sequence of the complementary determining region (CDR) of the antibody's heavy and light chain subunits and the substitution of a single amino acid in the sequence significantly reduces its ability to bind to the antigen. Applicant has not made a single antibody to the modified I-domain opened conformation, that would result in an antibody that would specifically binds to the modified I-domain but not wild type I-domain (whether open or closed). Applicant has not compare antibodies to modified I-domain in open conformation to modified I-domain in closed conformation. Applicant relies on screening of pre-existing antibodies to the I-domain which would be expected to give the results presented in table 3. Applicant compared the antibodies to wild type unmodified I-domain.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 25-27, 29-30, 73-80 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6, in view of U.S. Patent No. 5,843,712.

Huang *et al* teach five monoclonal antibodies BL5, F8.8, May.035, TS1/22 and TS2/6 which selectively bind to an integrin I-domain (see page 3163 under mAbs and Cell Lines, and page 3164 Figure 2 in particular). Those antibodies bind to specific epitope on the integrin α L subunit of I-domain of LFA-1 integrin (page 3164 Figure 2 in particular). Although Huang *et al* do not teach the specific antibodies bind to a modified I-domain of α L subunit containing amino acid substitutions E284C/E301C, wherein the modified integrin polypeptide is stabilized in the open conformation. These limitations are considered an inherent property of the reference antibodies.

As is evidenced by Lu *et al*, that antibodies against α L I domain of LFA-1, BL5, F8.8, May.035, TS1/22 and TS2/6 bind to the open or "active" mutants K287C/K294C of α L subunit of LFA-1 "modified I domain" (see Table 1 page 2394 in particular). Furthermore, Lu *et al* teach that BL5, F8.8, May.035, TS1/22 and TS2/6 antibodies strongly inhibited binding of both wild-type and mutant K287C/K294C of α L subunit of LFA-1 (page 2395, Table 2 in particular). Lu *et al* compare the binding of modified integrin I-domain in the open conformation (K287C/K294C) relative to the modified integrin I-domain in the closed conformation (L289C/K294C) as well as (see table 1 in particular) the wild type. The binding to the open and closed conformation mutants is almost equivalent among the antibodies or differs by only a few percentage points.

Further, as is evidenced by the specification on page 76, lines 7-8 and page 77, Table 6 that the affinity of E284C/E301C mutant is nearly comparable to K287C/K294C mutant affinity (e.g. predicted open conformation binds with high affinity).

The claimed invention differs from the reference teachings only by the recitation of a recombinant antibody, the antibody comprises a portion of human antibody and a portion of a non-human antibody in claim 76, a humanized antibody in claim 77, and a chimeric antibody in claim 78.

The '712 patent teaches that the expression of recombinant antibodies in mammalian cells offers great advantages with respect to post-translational modifications, stability, immunogenicity, and yields (see column 1, lines 40-45 in particular), wherein Sindbis virus vectors offer a powerful tool for the rapid production of genetically engineered antibodies (column 1m lines 1, lines 48-56 in particular). The '712 patent further teaches that the Sindbis virus vector system can be useful to produce recombinant antibodies that replace immunoglobulin therapies that are presently being used in the treatment of certain inflammatory disorders, immunodeficiency states, and viral infections. The advantages of such recombinant antibodies (versus serum immunoglobulin therapy MAbs derived from mouse hybridoma cells) would be that they can easily be humanized. Further these antibodies can be custom designed to modify their specificity, and produced in very large quantities (see column 16, lines 8-16 in particular). Finally, the '712 patent teaches that the Sindbis virus vector system can easily be adapted to

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produce chimeric, humanized or human antibodies. The feasibility of producing high yields of humanized biologically active antibodies suggests that the Sindbis virus vector system can be useful for the generation of therapeutic antibodies. Results demonstrate that an antibody produced using the Sindbis virus vector system is able to protect mice against a lethal infection of the central nervous system (see column 15 lines 66-67 and column 16 lines 1-8 in particular).

Claim 80 is included because antibody is antibody irrespective of how it's made.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the antibodies taught by Huang *et al* recombinantly, chimeric, humanized or human taught by the '712 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the recombinant antibody offers great advantages with respect to post-translational modifications, stability, immunogenicity, and yields as taught by the '712 patent. Further, chimeric, humanized are human antibodies can be useful for the as therapeutic antibodies as taught by the '712 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 8/06/03 have been fully considered, but have not been found convincing.

Applicant asserts that the prior art teaches antibodies bind to open or active mutants of αL with at least some affinity. Applicant contends that the amended claims require something significantly different than merely binding to an integrin in the open conformation. Applicant points out that claims 25-30, 73-80 and 82 require that the binding be specific for the open conformation relative to the closed conformation. Applicant asserts that table 1 of Lu et al does not show antibody having the claimed properties. Applicant contends that the binding to the open or closed conformational mutants is almost equivalent among the antibodies or differs by only a few percentage points.

mAb	K287C/K294C [open conformation]		L289C/K294C [closed conformation]	
	293T	K562	293T	K562
BL5	92 ± 11	92	86 ± 16	98
F8.8	94	102	84	94
TS2/6	85 ± 6	89	79 ± 3	96
May.035	93 ± 8	93	82 ± 14	101
TS1/22	96 ± 12	93	91 ± 8	110

Contrary to applicant's assertions, table 1 of Lu et al compare the antibodies binding to modified integrin I-domain in the open conformation (K287C/K294C) relative to a modified integrin I-domain in the closed conformation (L289C/K294C) as well as to an integrin I-domain in the closed conformation (wild type) (see table 2 page 2395 in particular). Therefore, the antibodies taught by Huang et al meet the claimed limitation that the antibodies bind specifically to a modified integrin I-domain in the open conformation relative to a modified integrin-Domain in the closed conformation/relative to an integrin I-domain in the closed conformation.

Applicant argues that the cell-to-cell differences for binding to the closed conformation and the cell-cell differences for binding to the open conformation are of similar magnitude as the differences between binding the open and closed conformation for the same cells-type. However, the comparison is still relative between open (modified) and closed (modified and unmodified).

12. Claims 25-27, 29-30, 73-80 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6 in view of U.S. Patent No. 5,843,712 and further in view of Owens *et al* (1994).

The teachings of Huang *et al*, Lu *et al* cited as an evidentiary reference and the '712 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of an antigen binding fragment.

Owens *et al* teach the modification of murine antibodies such as a single chain antibody, a Fab fragment, or a F(ab')₂ fragment. Owens *et al* further teach antibody fragments are the reagents of choice for some clinical applications (see the entire document).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the antibodies taught by Huang *et al* as Fab and F(ab')₂ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6 in view of U.S. Patent No. 5,843,712 as applied to claims 25-27, 29-30, 73-80 and 82 above, and further in view of U.S Patent No. 6,413,963.

The teachings of Huang *et al*, Lu *et al* cited as an evidentiary reference and the '712 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition and a pharmaceutically acceptable carrier.

The '963 patent teaches pharmaceutical compositions prepared comprise a therapeutically effective amount of a compound (e.g. antibody) in a pharmaceutically acceptable carrier. The '963 patent further teaches that therapy with inhibitors of cell adhesion are indicated for any condition in which an excess of integrin-mediated cell adhesion is a contributing factor (see column 18, lines 28-41 and column 20 lines 11-12 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the antibodies taught by Huang *et al* reference in a pharmaceutical compositions in a pharmaceutically acceptable carrier taught by the '963 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because antibody pharmaceutical compositions are used in a therapy where any condition in which an excess of integrin-mediated cell adhesion is a contributing factor as taught by '963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6, in view of U.S. Patent No. 5,843,712 and further in view of Owens et al as applied to claims 25-27, 29-30, 73-80 and 82 above, and further in view of U.S Patent No. 6,413,963.

The teachings of Huang *et al*, Owens *et al*, Lu *et al* cited as an evidentiary reference and the '712 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of that the antigen binding fragment further comprising a pharmaceutically acceptable carrier.

The '963 patent teaches pharmaceutical compositions prepared comprise a therapeutically effective amount of a compound (e.g. antibody) in a pharmaceutically acceptable carrier. The '963 patent further teaches that therapy with inhibitors of cell adhesion are indicated for any condition in which an excess of integrin-mediated cell adhesion is a contributing factor (see column 18, lines 28-41 and column 20 lines 11-12 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the antigen binding fragment taught by Huang *et al* in view of Owens et al in a pharmaceutical compositions comprising a pharmaceutically acceptable carrier taught by the '963 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because antibody pharmaceutical compositions are used in a therapy where any condition in which an excess of integrin-mediated cell adhesion is a contributing factor as taught by '963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
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November 28, 2003


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